Support for the amendments is found in the specification and the originally filed claims, e.g. page 19, line 1 (immunodetection assay); page 2, lines 18-19 (suspected of toxicity); Examples 2 and 3 (sets of genes and protein); page 7, lines 26-30 (pattern of alterations in gene expression or protein expression); and examples 2 and 3 (unmodified embryoid body).

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached pages are captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

Interview and Information Disclosure Statement

Applicants thank the Examiner for extending the courtesy of the helpful telephone interview with Applicant's representative, on November 28, 2001 with Primary Examiner Clark. This response reflects the results of that interview.

Applicant respectfully points out that the Examiner has not acknowledged or initialed the Form 1449s enclosed with the two supplemental information disclosure statements submitted August 29, 2000 and November 16, 2000. Applicant further notes that another supplemental information disclosure statement is being filed herewith. Applicant respectfully requests that the Examiner acknowledge receipt of the 1449s by initially and returning the Forms to Applicant.

Concerning priority

Applicant notes that the specification has been amended to recite a specific reference to an earlier filed application (U.S. Provisional Application Serial No. 60/111,640, filed December 9, 1998) to which applicant desires priority under 35 U.S.C. 119(e).

Rejection of claims under 35 U.S.C. § 112, first paragraph

Claims 1-18 and 21-33 stand rejected under 35 U.S.C. § 112, first paragraph allegedly because the specification, while being enabling for isolating embryonic stem cells to generate embryoid bodies from species in which embryonic stem cells have been known to be isolated, does not reasonably provide enablement for generating embryoid bodies from embryonic stem cells from species in which such cells have been previously isolated. In addition, the Examiner states that the specification is allegedly not enabling of the claim-designated methods of detecting changes in protein and gene expression in embryoid bodies. Applicant respectfully traverses this rejection.

Applicant respectfully submits that the specification discloses methods for obtaining embryonic stem cells and embryoid bodies from humans, as well as other species (including mice, primates, and pigs). Applicants respectfully direct the Examiner's attention to pages 12-14 of the specification, which discuss preparing embryonic bodies. Specifically, the isolation of human embryonic stem cells and the formation of human embryoid bodies is described at page 13, line 21 through page 14, line 22, and the isolation of embryonic stem cells and preparation of embryoid bodies from primates, mouse, pig, and other stem cells is described at page 12, line 2 through page 13, line 20. Thus, it is evident that the specification provides guidance as to how to obtain human embryonic stem cells and embryoid bodies; and provides guidance as to obtain embryonic stem cells and embryoid bodies from several species, including primates, human, pig and mouse, and that such methods were well known in the art at the time this application was filed.

Applicant notes that the Examiner relies on the Seamark and Matsui references in support of the enablement rejection in support of her assertion that "embryonic stem cell technology has not advanced such that isolation of embryonic stem cells from any mammalian species is routine and predictable. Office Action, page 3. Applicant respectfully submits that Seamark, published in 1992, and Matsui, published in 1994, are not relevant evidence as to the state of the art of the present application, which claims priority to an application filed in December of 1998. Moreover, as discussed above, the specification discloses methods for obtaining embryonic stem cells and embryoid bodies from humans, as well as other species (including mice, primates, and pigs). Thus, Applicant submits that the specification fully enables the isolation of mammalian embryonic stem cells. Prompt withdrawal of this rejection is respectfully requested.

The Examiner also asserts that the specification is allegedly not enabling of the "methods of detecting changes in protein and gene expression in embryoid bodies", because the specification "does not provide any guidance as to how to record alterations in gene expression or protein expression in the mammalian embryoid body". Office Action, page 3. Specifically, the Examiner note that "the specification does not provide sufficient guidance to detect alterations in gene expression by a nucleotide hybridization assay, or alterations in protein expression by an "immunoactivity" assay, such that the detecting methods are sufficiently reproducible." Office Action, page 4. The Examiner further asserts that, while the specification generally teaches that methods of monitoring gene and protein expression are known in the art, the specification allegedly "lacks guidance . . . as to how to utilize these methods of monitoring for the purpose of creating a molecular profile, or compiling a library of molecular profiles or for typing toxicity of a test chemical composition." Id. Applicant traverses.

As a preliminary matter, Applicant notes that claims 1, 2 and 21-23 have been amended to recite "detecting and recording alterations in expression of sets of gene or proteins", and to further recites that the alterations in gene expression or protein expression in the mammalian embryoid body contacted with the chemical composition are compared to gene expression or protein expression in an embryoid body not contacted with the chemical composition, as further

discussed below. Applicant believes that this amendment addresses the Examiner's concern that one skilled in the art "would not know that changes in gene or protein expression have occurred". See Office Action, page 4. During the interview, Examiner Clark reacted favorably to this amendment.

Applicant also notes that claims 1, 2, and 21-23 have been amended to recite "a pattern of alterations" or "pattern of alterations in gene expression or protein expression in the mammalian embryoid body in response to", instead of "molecular profile" or "molecular profile of", as further discussed below. Claim 8 has been amended to recite "immunodetection" assay instead of "immunoactivity" assay, as further discussed below. Applicant will address the enablement rejection as applied to the claims as amended in this response.

Applicant submits that methods of detecting a pattern of alterations sets of genes and proteins, including nucleotide hybridization and detection of protein using immunodetection assays, are well known in the art. Methods for performing these techniques are set out in many sources, including such standard works as the cloning manuals, *Molecular Cloning: A Laboratory Manual* by Sambrook et al. (1989) and *Current Protocols in Molecular Biology* by Ausubel et al. (1987). The compilation of these methods in such standard cloning manuals demonstrates that these techniques are well established in the art and are not unpredictable. Applicant need not describe what is known in the art.

Moreover, Applicant respectfully submits that the specification provides ample guidance to one skilled in the art to carry out the invention. Applicant notes that the specification provides ample and detailed guidance regarding methods of detecting alterations in gene expression and protein expression. Thus the specification provides ample guidance on methods of detecting alterations in expression of sets of proteins (page 18, line 10 through page 20, line 10; Example 2); methods of detecting alterations in expression of sets of genes (page 20, line 17, through page 23, line 28; Example 3); use of array readers and high-throughput screening methods (page 29, line 23 through page 30, line 22), correlating pattern of alterations in expression of sets of gene or proteins (page 26, line 1 through page 27, line 3), and typing and ranking toxicities of test

chemical compositions (page 27, line 7 through page 30, line 2), and methods of recording and comparing alterations in gene and protein expression (for example, page 27, line 22 through page 30, line 2). Applicant respectfully submits that the guidance provided is more than adequate to allow one of ordinary skill in the art to carry out the invention.

The law is clear that a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as satisfying the enablement requirement unless there is reason to doubt the objective truth of the teachings of the specification. *In re Marzocchi*, 169 USPQ 367,369 (CCPA 1971). It is incumbent upon the Examiner to explain why one skilled in the art would doubt the truth of statements made in the specification, and to back up assertions with acceptable and specific evidence. Id. at 370. Absent evidence to the contrary, the specification must be assumed to be enabling. Because the Examiner has failed to provide acceptable and specific evidence to support the contentions that the specification does not provide sufficient guidance to detect alterations in gene expression by nucleic acid hybridization assay or alterations in protein expression by an immunodetection assay, or that the detecting methods are not consistent and reproducible, the specification must be assumed to be enabling. Accordingly, withdrawal of this rejection is respectfully requested.

The Examiner also states in this rejection that, with respect to the mass spectrometry assays, "no correlation is [disclosed] in the specification between changes in protein expression and toxicity *per se*." Office Action, pages 3-4. The Examiner also relies on the Flint article in support of the argument that "gene chip technology for identify compound-specific patterns of induction", while useful, allegedly faces "significant hurdles". Office Action, page 4.

To the extent that the Examiner relies on these argument in the rejection of claims 1-18, Applicant respectfully submits that this is improper. Applicant points out that claims 1-18 recite methods of creating molecular profiles, and methods of compiling a library of molecular profiles. These claims are not directed to methods of typing toxicity, and further do not require comparing the molecular profile in step a) with the molecular profile of a chemical composition having predetermined toxicities, wherein the type of toxicity of the test chemical composition is

determined by the comparison (as required by claim 21); comparing the molecular profile in step a) with a composite library of molecular profiles of chemical compositions having predetermined toxicities . . . wherein the type of toxicity of the test chemical composition is determined by the comparison (as required by claim 22); or comparing the molecular profile in step a) with a composite library of chemical compositions having predetermined toxicities . . . wherein the toxicity of the test chemical composition is ranked by the comparison (as required by claim 23). Therefore, Applicant respectfully submits that the alleged absence of "a correlation between changes in protein expression and toxicity", and the alleged lack of validation of gene chip technology for identify compound-specific patterns of induction, have no bearing on the issue of the enablement of claims 1-18. Accordingly, withdrawal of this rejection is respectfully requested.

With respect to the Examiner's assertion that "no correlation is [disclosed] in the specification between changes in protein expression and toxicity *per se*", Applicant submits that methods of comparison are well known and routinely used. Furthermore, the guidance provided in the specification is more than adequate to allow one of ordinary skill in the art to carry out the invention. For example, the specification teaches that the comparison of gene or protein expression with toxicities can be performed by any convenient means, including visual comparison of patterns to determine patterns associated with different types of toxicity, database programs or neural networks, or informatics programs such as Spot-Fire or Gene Spring. See, e.g., the specification at page 26, line 1 through page 27, line 2; page 29, lines 4-21; Example 3 (passim).

Applicant further submits that the Examiner's reliance on the Flint article is misdirected, for Flint's conclusion (as cited by the Examiner) relies on assumptions about methods of identifying compound-specific patterns of gene induction which do not apply to the invention of claims 21-23. First, Flint focuses on the shortcomings of expression testing using cultured cell lines, speculating that this method of analysis will require "substantial effort" and moreover, that patterns of gene induction may vary according to the cell type selected for culture. *See* Flint,

page 592, left column. By contrast, the present invention provides methods of assessing toxicity of chemical compositions on a genome-wide basis, in a system that closely models the complex biological and cellular interactions of whole organisms, including the human body, because, for example, embryoid bodies represent a complex group of cells differentiating into different tissues. Thus, the cells within embryoid bodies provide a much closer model to the complexity of whole organisms than do traditional single cell or yeast assays, while still avoiding the cost and difficulties associated with the use of mice and larger mammals. Thus, the present invention does not suffer from the shortcomings relied upon by Flint.

Second, Flint relies on the proposition that "insufficient chemicals with well-characterized toxicity profiles are available", and that there is poor availability of "good" toxicology data for purposes of generating compound-specific patterns of gene induction. Id., page 592, left column. As an example of "good toxicity data", Flint points to animal testing, including histopathological analysis of a group of 10 "toxicologically significant organs". Id. By contrast, the methods of claims 21-23 do not require the use of chemical composition for which exhaustive animal testing has been performed (though such compounds may be used in the methods). For example, suitable chemical compounds include thousands of compounds that have undergone preclinical and clinical studies. See, e.g., specification, page 9, line 30 to page 10, line 5. Indeed, the specification points out that a considerable amount of information is available about the toxicity of various of these compounds. Accordingly, Applicant respectfully submits that the alleged shortcoming relied upon by Flint does not apply to the methods of claims 21-23.

In summary, Applicants respectfully submits that the specification teaches methods of monitoring expression of sets of genes or proteins, and how to use these well known methods for the purpose of creating a molecular profile, compiling a library of molecular profiles and typing toxicity of a test chemical composition. As such, Applicant submits that claims 1-18 and 21-33 are fully enabled. For the reasons stated above, Applicant respectfully requests withdrawal of this rejection.

Rejection of claims under 35 U.S.C. § 112, second paragraph

Claims 1-18 and 21-33 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant traverses these rejections.

(a) Claims 1, 2 and 21-23 are allegedly indefinite for reciting the phrase "a molecular profile," because it is allegedly unclear what the phrase means. The Examiner further states that it is also "unclear how the alterations in gene expression or protein expression in the mammalian embryoid body are recorded." Office Action, page 5. Applicant respectfully disagrees that the phrase "a molecular profile" renders claims 1, 2, and 21-23 unclear. Applicant directs the Examiner's attention to the specification at page 7, lines 27-30, where "molecular profile" is defined as "a pattern of alterations in gene or protein expression, or both, in an embryoid body contacted by the chemical composition compared to a like embryoid body in contact only with culture medium." Applicant submits that the meaning of "molecular profile" is clear and prompt withdrawal of this rejection is respectfully requested. However, to expedite prosecution, claims 1, 2, and 21-23 have been amended in selected portions to recite "a pattern of alterations" or "pattern of alterations in gene expression or protein expression in the mammalian embryoid body in response to", instead of "molecular profile" or "molecular profile of". Applicants submits that these amendments obviate the ground for the rejection. During the Interview, Primary Examiner Clark reacted favorably to this amendment. Withdrawal of this rejection is respectfully requested.

Applicants note that the Examiner further questions "how alterations in gene expression or protein expression in the mammalian embryoid body are recorded." Office Action, page 5. To the extent that the Examiner relies on this assertion in the indefiniteness rejection of these claims, Applicant submits that one skilled in the art could readily ascertain the scope of these claims. The legal standard for indefiniteness is whether those skilled in the art would understand what is claimed when the claim is read in light of the specification. *Orthokinetics, Inc. v. Safety*

Travel Chairs, Inc., 806 F.2d 1565, 1576 (Fed. Cir. 1986) (citations omitted) (*accord, Morton International, Inc. v. Cardinal Chemical Company*, 5 F.3d 1464, 1470 (Fed. Cir. 1993)). Applicant points out that the specification teaches that the determination of alterations in expression of sets of genes or sets of proteins is routine and known in the art, and further discloses many methods for monitoring alterations in gene or protein expression, as discussed above with respect to the enablement rejection. Accordingly, one skilled in the art readily understands how to ascertain alterations in gene and/or protein expression using a variety of methods, and thus, the scope of these claims would understand what is claimed when the claim is read in light of the specification. As such, Applicant submits that the scope of these claims is clear. Withdrawal of this rejection is respectfully requested.

(b) Claim 8 is allegedly vague and indefinite for reciting the phrase "immunoactivity assay", as it is allegedly unclear what type of assay this encompasses. Applicant disagrees that the phrase "immunoactivity assay" renders claim 8 vague. However, to expedite prosecution, claim 8 has been amended to replace "immunoactivity assay" with "immunodetection assay." Support for the term "immunodetection" is found on page 19, line 1. Applicant believes that this amendment clarifies that the assay encompassed by these claims is an immunodetection assay, not an assay of the activity of a population of immune cells as suggested by the Examiner. See Office Action, page 5. During the Interview, Primary Examiner Clark reacted favorably to this amendment.

(c) Claim 23 is allegedly indefinite for reciting the phrase "ranking toxicity" because it is allegedly unclear "if the composition is ranked relative to its toxicity or relative to the cells that are affected by the composition." Office Action, page 5. Claims 21 and 22 are allegedly indefinite for reciting the phrase "type of toxicity". See *id.* Applicant respectfully traverses this rejection.

Applicant disagrees that the meanings of "type of toxicity" and "ranking toxicity" are unclear. Applicant note that these terms have an art-recognized meanings. For example, "type of toxicity" generally refers to the category of toxicity, for example, the tissues or organs in

which the toxicity is exerted or developmental toxicity as exemplified in Table 1 (page 10) and Table 2 (page 37). "Ranking toxicity" generally refers to determining a relative order (or rank) of chemical with respect to severity of the toxicity of the chemicals. Applicants submit that this art-recognized usage is implicit in the use of the terms in the specification, for example, specification at page 7, lines 10-25 (defining toxicity); page 12, lines 1-4 (comparing toxicity typing and ranking); page 28, lines 16-29 (same). Withdrawal of this rejection is respectfully requested.

Rejection of claims under 35 U.S.C. § 102(b)

Ling et al.

Claim 1, 3 and 4 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Ling et al. (J. Cell. Phys., 171:104-115, 1997). Ling et al. is cited for allegedly disclosing a method of contacting an isolated mammalian embryoid body with a chemical composition comprising LIF, IL-11 or IL-6, and recording alterations in protein expression using fluorescent label. Applicant respectfully traverses.

Claim 1 has been amended to recite "[a] method of creating a molecular profile of a chemical composition suspected of toxicity, and the phrase "suspected of toxicity" has also been inserted into clause (a) of the claims. By contrast, Ling et al. describe contacting embryoid bodies with growth factors (LIF, IL11 or IL-6). Applicant submits that growth factors as administered by Ling et al. would not be viewed as having potential toxicity. Furthermore, Applicant respectfully submits that Ling et al did not expose the embryoid bodies to growth factors in order to test for potential toxic effect of growth factors. Rather, Ling et al. exposed embryoid bodies to growth factors in order to quantify the kinetics of embryoid body differentiation. See, e.g., page 105, left column, first full paragraph; abstract.

Because Ling et al. does not teach the administration of a chemical composition suspected of toxicity, Ling et al. do not anticipate claims 1, 3 and 4. Withdrawal of this rejection is respectfully requested.

Spielmann et al.

Claims 1, 2-4, 7, 14-18, 21-24, and 29-33 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Spielmann et al. (In Vitro Toxicity, 10:119-127, 1997). Spielmann is cited as allegedly teaching a method for determining the cytotoxicity of the chemical compositions by "changes in protein expression, i.e., via the MTT cytotoxicity assay." Office Action, page 7. Applicant respectfully traverses.

Applicants respectfully point out that claims 1, 2, and 21-23 have been amended to recite "detecting and recording alterations in expression of sets of gene or proteins".

As a preliminary matter, Applicant respectfully point out that Spielmann et al. use embryonic stem cells, kept in an undifferentiated state, for the cytotoxicity screening assay. See page 120, last paragraph through page 121, first paragraph (describing the ES cell cytotoxicity method); see also page 120, paragraph entitled "cell culture conditions (describing the maintenance of embryonic stem cells in the undifferentiated stated by the addition of LIF); compare with page 121, paragraph entitled "in vitro differentiation of D3 embryonic stem cells into contracting myocardial cells" (describing the induction of cell differentiation using the hanging drop method in the presence of FBS).[1] Thus, the Spielmann cytotoxicity assay of embryonic stem cells does not involve "contacting a mammalian embryoid body" as required by claims 1, 2, and 21-23. Accordingly, Spielmann et al do not anticipate claims 1, 2-4, 7, 14-18, 21-24, and 29-33. Applicant respectfully requests withdrawal of this rejection.

Moreover, the MTT cytotoxicity test is not a method of detecting alterations in expression of sets of genes or proteins, as required by claims 1, 2, and 21-23. The MTT cytotoxicity test is used to detect dead embryonic stem cells, and, indeed, Spielmann et al.

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[1] Applicants point out that Figure 1 of Spielmann (on page 120) does not describe the method cited by the Examiner for determining the cytotoxicity of chemical compositions by measure ES cell death via the MTT cytotoxicity test. Rather, this figure describes Spielmann's cell differentiation assay, which is a completely different assay that the ES cell cytotoxicity assay cited in this rejection. As such, this figure is not pertinent to the grounds asserted in the Examiner's rejection.

merely counted the number of dead or alive embryonic stem cell colonies following exposure to the tested chemical compounds. Because Spielmann does not teach a method of detecting alterations in expression of sets of genes or proteins, Spielmann cannot anticipate claims 1, 2, and 21-23. Accordingly, Applicant respectfully requests withdrawal of this rejection.

Applicant notes that Spielmann also describes a toxicity assay using embryoid bodies as follows: embryoid bodies are contacted with a chemical compound, and the presence or absence of embryoid bodies with beating heart muscle is determined by visual inspection. *See* Fig. 1; page 121. However, the visual inspection of embryoid bodies for the presence or absence of beating heart muscle is not a method of detecting alterations in expression of sets of genes or proteins as required by claims 1, 2, and 21-23. Accordingly, Spielmann does not anticipate claims 1, 2-4, 7, 14-18, 21-24, and 29-33. Prompt withdrawal of this rejection is respectfully requested.

Applicant points out that the Examiner did not state in the rejection that Spielmann teaches the subject matter recited in the rejected dependent claims. For the record, Applicant disagrees that Spielmann teaches that the detection of alterations in gene expression or protein expression are detected by a label (claims 3 and 4); that that the molecular profile comprises alterations in protein expression (claim 7); and that the chemical compositions are selected from the groups listed in claims 16, 18, 26, 28, 31 or 33.

For the reasons stated above, Applicant respectfully requests withdrawal of this rejection.

Rejection of claims under 35 U.S.C. § 102(e)

Claims 1, 3-5 and 7 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Wobus et al (US Patent No. 6,007,993, 1999, with an effective filing date of 2/24/98). Applicants respectfully traverse.

Claim 1 has been amended to recite that the embryoid body is unmodified. By contrast, Wobus et al. disclose the use of transgenic embryonic stem cell clones. Thus, Wobus does not

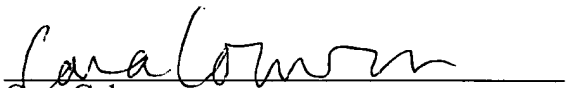
anticipate claim 1 (and claims 3-5 and 7 which depend from claim 1). Accordingly, Applicants respectfully request withdrawal of this rejection.

CONCLUSION

Applicant has, by way of the amendments and remarks presented herein, made a sincere effort to overcome the rejections and address all issues that were raised in the outstanding Office Action. Accordingly, reconsideration and allowance of the pending claims are respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 441472000100. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: December 18, 2001 By: 

Cara Coburn
Reg. No. 46,631

for Gladys H. Monroy
Reg. No. 32,430

Morrison & Foerster LLP
755 Page Mill Road
Palo Alto, California 94304-1018
Telephone: (650) 813-4218
Facsimile: (650) 494-0792

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

CROSS-REFERENCES TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 60/111,640, filed December 9, 1998, the disclosure of which is incorporated herein by reference.

In the Claims:

3. (Amended) A method of creating a molecular profile of a chemical composition suspected of toxicity, comprising the steps of:

a) contacting an isolated unmodified mammalian embryoid body with the chemical composition suspected of toxicity; and

b) detecting and recording alterations in expression of sets of genes or proteins[gene expression or protein expression] in the mammalian embryoid body in response to the chemical composition compared to expression of sets of genes or proteins in an embryoid body not contacted with the chemical composition, to create a [molecular profile of] pattern of alterations in gene expression or protein expression in the mammalian embryoid body in response to the chemical composition.

4. (Amended) A method of compiling a library of molecular profiles of chemical compositions having predetermined toxicities, comprising the steps of:

a) contacting an isolated mammalian embryoid body with a chemical composition having predetermined toxicities;

b) detecting and recording alterations in expression of sets of genes or proteins[gene expression or protein expression] in the mammalian embryoid body in response to the chemical composition compared to expression of sets of genes or proteins in an embryoid body not contacted with the chemical composition, to create a [molecular profile of]pattern of alterations in gene expression or protein expression in the mammalian embryoid body in response to the chemical composition; and

c) compiling a library of molecular profiles by repeating steps a) and b) with at least two chemical compositions having predetermined toxicities.

8. The method of claim 7, wherein the alterations in protein expression are detected by an [immunoactivity]immunodetection assay.

21. (Amended) A method of typing toxicity of a test chemical composition, comprising the steps of:

a) creating a molecular profile of the test chemical composition [according to claim 1], comprising the steps of:

i) contacting an isolated mammalian embryoid body with the chemical composition; and

ii) detecting and recording alterations in expression of sets of genes or proteins in the mammalian embryoid body in response to the chemical composition compared to expression of sets of genes or proteins in an embryoid body not contacted with the chemical composition, to create a pattern of alterations in gene expression or protein expression ; and

b) comparing the molecular profile in step a) with the molecular profile of a chemical composition having predetermined toxicities;

wherein the type of toxicity of the test chemical composition is determined by the comparison in step b).

22. (Amended) A systematic method of typing toxicity of a test chemical composition, comprising the steps of:

a) creating a molecular profile of the test chemical composition[according to claim 1], comprising the steps of:

i) contacting an isolated mammalian embryoid body with the chemical composition; and

ii) detecting and recording alterations in expression of sets of genes or proteins in the mammalian embryoid body in response to the chemical composition compared to expression

of sets of genes or proteins in an embryoid body not contacted with the chemical composition, to create a pattern of alterations in gene expression or protein expression; and

b) comparing the molecular profile in step a) with a composite library of molecular profiles of chemical compositions having predetermined toxicities, wherein the composite library comprises the molecular profiles of at least two chemical compositions, wherein said molecular profiles are created according to claim [1]2;

wherein the type of toxicity of the test chemical composition is determined by the comparison in step b).

23. (Amended) A method of ranking toxicity of a test chemical composition, the method comprising:

a) creating a molecular profile of the test chemical composition [according to claim 1], comprising the steps of:

i) contacting an isolated mammalian embryoid body with the chemical composition; and

ii) detecting and recording alterations in expression of sets of genes or proteins in the mammalian embryoid body in response to the chemical composition compared to expression of sets of genes or proteins in an embryoid body not contacted with the chemical composition, to create a pattern of alterations in gene expression or protein expression; and

b) comparing the molecular profile in step a) with a composite library of molecular profiles of chemical compositions having predetermined toxicities, wherein the composite library comprises the molecular profiles of at least two chemical compositions, wherein said molecular profiles are created according to claim [1]2;

wherein the toxicity of the test chemical composition is ranked by the comparison in step b).